

### **REMARKS**

In the Office Action dated September 9, 2003, Claims 3-4 and 15-32 are pending and under consideration. Claims 27-28 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 3-4 and 15-32 are rejected under 35 U.S.C. §101 allegedly because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility. Claims 3-4 and 15-32 are also rejected under 35 U.S.C. §112, first paragraph. Claims 3-4 and 15-32 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the written description requirement. Claims 3-4, 16, 18 and 20 are rejected under 35 U.S.C. §102(a) as allegedly anticipated by Young et al. (Jan. 2000) (GenBank Accession No. AJ011374.1). Claim 15 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Young et al. in view of U.S. Patent No. 6,180,608. The application is also objected to for certain alleged informalities. The Amendment filed April 17, 2001 remains objected to under 35 U.S.C. §132 allegedly because it introduces new matter into the disclosure.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

The oath is objected to as defective, because the oath does not refer to the Preliminary Amendment filed on April 17, 2001. The amendment filed April 17, 2001 is objected to under 35 U.S.C. §132, allegedly because it introduces new matter into the disclosure. The Examiner states that the reference to U.S. application Serial No. 60/200,040, which was added on page 1 of the specification by way of the Preliminary Amendment, does not enjoy the status as part of the original disclosure in the application because the Amendment was not referred to in the oath.

Applicants will submit a new oath to refer to the Preliminary Amendment in due course.

The Examiner has also objected to the drawings submitted on June 18, 2003. Applicants will submit corrected formal drawings in due course.

The Examiner has also objected to the specification because it contains an embedded hyperlink and/or other form of browser-executable code on page 1, lines 13. In response, Applicants have amended the specification to delete the embedded hyperlink. Withdrawal of the objection to the specification is therefore respectfully submitted.

By way of the instant amendment, Applicants have canceled claims 3-4 and 15-32. Applicants reserve the right to pursue the subject matter of these claims in a continuation application. Applicants have also added claims 33-37. Support for these new claims is found in original claims 3-4. No new matter is introduced.

Claims 27-28 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite, for reciting "or combinations or such changes".

Applicants respectfully submit that the rejection is rendered moot in view of cancellation of claims 27-28. Applicants further submit that new claims 33-38 do not include the recitation "or combinations or such changes". Withdrawal of the rejection is therefore respectfully requested.

Claims 3-4 and 15-32 are rejected under 35 U.S.C. §101 allegedly because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The Examiner acknowledges that the specification asserts that the claimed ADAMTS protein exhibits anti-angiogenic and/or procollagen processing activities. The Examiner also

acknowledges that the specification asserts that the claimed protein can be used in the treatment of a number of diseases. In addition, the Examiner recognizes that the specification describes the functions of other ADAMTS proteins, such as ADAMST-1 and ADAMST-4, which are involved in fertility and organ development, for example. However, the Examiner contends that the asserted utilities of the claimed ADAMTS-M protein are not considered to be specific and substantial, allegedly because the specification fails to disclose any particular function or biological significance for ADAMTS-M. The Examiner alleges that the ADAMTS-M polypeptide is asserted to have a potential function based upon its amino acid sequence similarity to other known proteins. The Examiner contends that further research would be required to identify specific and substantial credible utility for the claimed ADAMTS-M protein, and that until such further characterization has been undertaken, the claimed invention is incomplete. In the Examiner's view, the instant situation is analogous to that which was addressed in *Brenner V. Manson*, 148 USPQ 689 (1966). The Examiner contends that the claims are drawn to a polypeptide of as yet undetermined function or biological significance, and that there is no evidence of record or any line of reasoning that would support a conclusion that the ADAMTS-M of the instant application was, as of the filing date, useful for the treatment of a disease as asserted.

Applicants respectfully submit that the rejection is rendered moot in view of cancellation of claims 3-4 and 15-32. Withdrawal of the rejection is therefore respectfully requested. However, Applicants address the grounds of the rejection as follows in light of added claims 33-38.

In the first instance, Applicants respectfully submit that the specification clearly describes the function and activities of the claimed ADAMTS-M polypeptide, contrary to the

Examiner's allegation. Specifically, the ADAMTS-M polypeptide is identified in the specification as a member of the ADAMTS family of metalloproteases – it is apparent that the ADAMTS-M polypeptide functions as a metalloprotease. As further described in the specification at page 14, lines 3-6, ADAMTS-M may have one or more specific proteolytic activities (e.g., collagenase, aggrecanase, procollagen protease), as well as anti-angiogenic activities.

Applicants further respectfully submit that the activities of the ADAMTS-M protein, identified in the specification, are supported by the significant degree of sequence similarity in the metalloprotease domain shared by the ADAMTS-S1 protein and other known polypeptides of the ADAMTS family, as described on page 14, lines 3-4 of the specification and illustrated in Figure 4. The asserted activities of the ADAMTS-M protein are also supported by the overall domain organization shared by the ADAMTS-S1 protein and other members of the ADAMTS family, as depicted in Figure 3. In light of these characterizations, the asserted activities of the ADAMTS-M protein would be considered credible by those skilled in the art.

Applicants further respectfully submit that the specification has also asserted a number of specific utilities of the ADAMTS-M protein, including employing the protein in the treatment of a number of disorders such as arthritis, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, ocular angiogenesis, among others.

In further support of the activities and the asserted utilities of the ADAMTS-M protein as described in the specification, Applicants provide herewith three articles: Gerritsen et al. (Blood 98: 1654-1661, 2001) (**Exhibit 1**); Fujikawa et al. (Blood 98: 1662-1666, 2001) (**Exhibit 2**); and Levy et al. (Nature 413: 488-494, 2001) (**Exhibit 3**).

Gerritsen et al. and Fujikawa et al. both identified an ADAMTS protein responsible for regulation of von Willebrand factor involved in blood clotting. The ADAMTS protein identified by Gerritsen et al. and Fujikawa et al. corresponds to ADAMTS-M disclosed in the present application. Gerritsen et al. and Fujikawa et al. identify the ADAMTS protein as responsible for continuous cleavage and degradation of plasma vWF multimers released from endothelial cells. According to Gerritsen et al., increased levels of vWF have been associated with atherogenesis, deep vein thrombosis, myocardial infarction and ischemic stroke (see page 1654, left column).

Levy et al. demonstrated that deficiency of ADAMTS13 (corresponding to ADAMTS-M of instant application) is responsible for thrombotic thrombocytopenic purpura (TTP), which disorder is characterized by decreased levels of proteolysis of vWF in patient plasma. Levy et al. indicate that ADAMTS-13 is essential for normal vascular homeostasis.

Applicants respectfully submit that the findings of Gerritsen et al., Fujikawa et al. and Levy et al. further support the protease activity of the ADAMTS-M as described in the present application, as well as the utilities of the ADAMTS-M protein asserted in the present application for treatment of disorders, particularly vascular disorders such as atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, ocular angiogenesis.

Accordingly, Applicants respectfully submit that the claimed invention is supported by a specific or substantial asserted utility. As such, the rejection under 35 U.S.C. §101 is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 3-4 and 15-32 are also rejected under 35 U.S.C. §112, first paragraph. The Examiner states that since the claimed invention is not supported by either a specific or

substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation. Furthermore, the Examiner contends that in the absence of a specific and detailed description of how to effectively use the pharmaceutical composition as claimed, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition. In addition, the Examiner contends that the description of one ADAMTS-M polypeptide in the specification is not a representative number of species to support the entire genus of functionally equivalent polypeptides as claimed, which encompass mutants, derivatives, variants and fragments having at least 90%, 95%, 97 or 99% identity to the amino acid sequences of SEQ ID NO: 2 or the specified domains thereof.

Applicants respectfully submit that the rejection is rendered moot in view of cancellation of claims 3-4 and 15-32. Applicants respectfully submit that added claims 33-38 are supported by a specific or substantial asserted utility, and those skilled in the art would be able to make and use the polypeptides as claimed in claims 33-38 without undue experimentation. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

Claims 3-4 and 15-32 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for the same reasons.

The Examiner acknowledges that the inventors were in possession of the polypeptide of SEQ ID NO: 2, as well as the metalloproteinase domain (aa 98-311 of SEQ ID NO:2), the disintegrin domain (aa 324-394 of SEQ ID NO:2), the prodomain (aa 1-97 of SEQ ID NO:2),

and the thrombospondin submotif (aa 410-473 and 1099-1156 of SEQ ID NO:2). However, the Examiner contends that the inventors were not in possession of the genus of polypeptides as claimed, which include variants having at least 90%, 95%, 97% or 99% sequence identity to SEQ ID NO: 2, or fragments of SEQ ID NO: 2, or having a substitution or deletion yet retaining the features essential to the ADAMTS-M protein.

Applicants respectfully submit that the rejection is rendered moot in view of cancellation of claims 3-4 and 15-32. Withdrawal of the rejection is therefore respectfully requested. Applicants further submit that new claims 33-38 are directed to the polypeptide of SEQ ID NO: 2 and the specific domains thereof which, as the Examiner has acknowledged, are adequately described in the specification.

Claims 3-4, 16, 18 and 20 are rejected under 35 U.S.C. §102(a) as allegedly anticipated by Young et al. (Jan. 2000) (GenBank Accession No. AJ011374.1).

Young et al. teach a polypeptide comprising an amino acid sequence having 100% identity to h amino acid sequence of thrombospondin submotif at positions 410-473. The term "comprising" in claims 3-4, 16, 18 and 20 is open ended, and thus the claims read on the polypeptide of 364 amino acids, disclosed by Young et al.

Applicants respectfully submit that the rejection is rendered moot in view of cancellation of claims 3-4, 16-18 and 20. Withdrawal of the rejection is therefore respectfully requested. Applicants further submit that new claims 33-37 are directed to the polypeptide of SEQ ID NO: 2 and the specific domains thereof. The polypeptide of claim 37 contains the thrombospondin submotif at positions 410-473 and 1099-1156. Applicants respectfully submit that Young et al. do not teach the polypeptides as presently claimed. Therefore, the rejection of

claims 3-4, 16, 18 and 20 under 35 U.S.C. §102(a) is overcome. Withdrawal of the rejection is respectfully requested.

Claim 15 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Young et al. in view of U.S. Patent No. 6,180,608.

The Examiner contends that the claimed invention differs from Young et al. only by the recitation of a pharmaceutical composition in claim 15, which includes a pharmaceutically acceptable carrier. The Examiner contends that the '608 patent teaches pharmaceutical compositions comprising a stable water-insoluble complex composed of a peptide compound and a carrier macromolecule. The '608 patent further purportedly discloses the advantages of the pharmaceutical compositions, e.g., its ability for delivery of a pharmaceutically active peptide, either systemically or locally, for prolonged periods. Thus, the Examiner concludes that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to include the polypeptide taught by Young et al. and a carrier as taught by the '608 patent in a pharmaceutical composition.

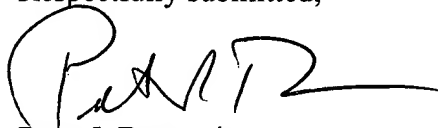
Applicants respectfully submit that the rejection is rendered moot in view of cancellation of claim 15. Withdrawal of the rejection is therefore respectfully requested.

Applicants further submit that new claim 38 is directed to a pharmaceutical composition comprising the polypeptide of any of claims 33-37 and a pharmaceutically-acceptable carrier. As submitted above, the polypeptides of claims 33-37 are not taught or suggested by Young et al. Therefore, claim 38 is not rendered obvious based on the combination of Young et al. and the '608 patent.



In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Peter I. Bernstein', with a long horizontal flourish extending to the right.

Peter I. Bernstein

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Encl: Exhibits 1-3